KEY WORDS
Dental implants, Early loading,
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Randomized controlled trial

OUTCOMES OF IMMEDIATE *VERSUS* EARLY IMPLANT LOADING IN PARTIALLY EDENTULOUS PATIENTS: 12-YEAR REPORT FROM A MULTICENTRE RANDOMIZED CONTROLLED TRIAL

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PURPOSE. To compare implant failure, complication rates and radiographic bone level changes of immediately- *versus* early-loaded non-occlusal dental implants in partially edentulous patients after 12 years of function.

MATERIALS AND METHODS. 80 partially edentulous patients requiring dual-implant-supported restorations were enrolled in this trial at five dental clinics. They were randomized into two equal groups (n=40) in order to receive implants loaded either immediately and non-occlusally (test group) or early (control group). To be included in the study, implants had to be inserted with torque ≥30 Ncm. Patients in the test group received immediately-loaded non-occlusal provisional restorations, while in the control group, healing abutments were attached and implants were left to heal unsubmerged. Definitive prostheses with full occlusal contact were fitted 2 months after surgery. The outcomes considered were implant failures, complications, and radiographic bone level changes.

RESULTS. Eighty-one implants were immediately loaded and 80 were early loaded. Twenty-five patients were lost before completion of the 12-year follow up: fourteen patients from the test group *versus* 11 patients from the control group. Two implants failed in the same patient from the control group. Four complications occurred in the test group and five complications occurred in the control group. There were no statistically significant differences between groups in terms of implant failures (patient level, 1/29 *vs.* 0/26, 3.4% *vs.* 0%, difference 3.4%; 95% CI: -0.5;7.3; P = 0.339) or complications (patient level, 4/26 *vs.* 5/29, 15.4% *vs.* 17.2%, difference 1.8%; 95% CI: -1.7;5.3; P = 0.853).
After 12 years, patients in the test group had lost an average of 1.41 mm (95% CI: 0.67, 2.05) of peri-implant bone *versus* 1.62 mm (95% CI: 0.96, 2.28) in patients from the control group. There were no statistically significant differences between immediate and early loading strategies in terms of peri-implant bone level changes (difference 0.21 mm; 95% CI -0.42, 0.84; P = 0.45). There were no statistically significant differences in clinical outcomes among centres.

CONCLUSIONS. Once adequate primary stability is achieved, no statistically significant difference in the outcomes considered was observed between immediately- and early-loaded implants up to 12 years after loading.

CONFLICT OF INTEREST STATEMENT
Tommaso Grandi serves as consultant for J Dental Care, Modena, Italy. However, this study was completely self-financed, and no funding was sought or obtained, not even in the form of free material.

INTRODUCTION

The original Bränemark protocol involved the use of a two-stage procedure in which the implant was first inserted into the jawbone and then kept load-free for a period of 3-4 months (in the mandible) or 4-6 months (in the maxilla). The stress-free healing period was deemed a prerequisite for the osseointegration of dental implants[1], but most patients perceive it as uncomfortable. Indeed, removable prostheses are normally prescribed during this healing period, but are not well accepted by patients, as most provide compromised function and aesthetics.

In recent years, therefore, implant-rehabilitation protocols have been improved, reducing treatment times and enabling dental implants to be loaded early, and even immediately, before osseointegration is complete[2,3]. This reduction in treatment time is beneficial for both patients and dentists, because from a patient's point of view a shorter healing period means less discomfort, and faster rehabilitation of masticatory function and aesthetics, while from the dentist's point of view, it saves chair-side time[4].

With the development of clinical techniques and implant surface modifications, a number of good-quality randomized controlled trials (RCTs) have reported high survival rates for immediate and early loading protocols, although not all authors have demonstrated predictably high success rates[5-9]. Moreover, there is little evidence in the literature on the long-term efficacy of different loading strategies.

Hence, the primary aim of this RCT was to provide long-term data on the outcomes of immediate non-occlusal loading *versus* early loading of implants in partially edentulous patients. Immediate non-occlusal loading was defined as an implant placed in function, immediately after insertion, with a provisional restoration that was not in contact with the opposing dentition. Early loading was defined as an implant placed in function after a 2-month healing period. This study is the continuation of two previous articles reporting results at 1 year[10] and 3 years[11] after loading. In this case, data were collected at 12 years post-loading. The outcomes considered were implant failure, prosthesis failure, complications and radiographic bone level changes. The present article is reported according to the CONSORT statement for improving the quality of reports on parallel-group randomized trials (http://www.consort-statement. org/).

MATERIALS AND METHODS

A total of 80 partially edentulous patients requiring a fixed restoration supported by two implants were recruited and randomly assigned to two groups: immediate (test group) *versus* early (control group) non-occlusal implant loading. All enrolled patients were randomized using a random number generator according to a parallel-group design. The allocation result was kept in a locked computer file that was not accessible to the investigators. The surgeons responsible for implant placement were informed by the study coordinator of individual allocations by e-mail or phone before surgery was performed. Each patient signed specific informed written consent.

Selection criteria

Patients were selected and included in the study according to the following criteria:

- Aged between 30 and 65 years;
- In need of a dual-implant-supported immediate restoration;
- Adequate oral hygiene, i.e., plaque index[12] ≤2;
- Sufficient bone volume to place implants at least 10 mm long and 3.7 mm in diameter.

Patients were not accepted into the study if they met any of the following criteria:

- Systemic disease that could compromise osseointegration;
- Treatment with radiation therapy in the craniofacial region within the previous 12 months;
- Previous or ongoing treatment with intravenous aminobisphosphonates;
- Uncontrolled diabetes;
- Substance abuse;
- Smoking more than 10 cigarettes per day;
- Pregnancy;
- Bruxism;
- Lack of opposing occluding dentition at the proposed implant site;
- Infection or severe inflammation in the area intended for implant placement;
- Need for bone augmentation procedures, including sinus augmentation.

During the first visit, PSR (Periodontal Screening and Recording) was used to evaluate the patient's oral hygiene and periodontal health. Patients with a PSR score of less than 3 were treated by a dental hygienist and subjected to PI (plaque index)[12] evaluation after 30 days. If the value of the PI was greater than 2, patients were not included in the study.
Patients were recruited and treated at five private dental clinics located in Italy, specifically: Modena (two centres), Bologna (two centres) and Rimini (one centre), all with extensive experience in the treatment of patients with early and immediate loading protocols. One experienced surgeon performed all of the operations at each centre. In cases of patients who needed restorations in multiple edentulous areas, the operator was free to choose at the screening visit one area to be included in the trial. Furthermore, the established protocol provided that implants should be inserted with a torque ≥30 Ncm, so if the implants did not reach that value of insertion torque, patients were not included in the study.

Clinical procedures

Pre-operative assessment of the anatomical features was performed on a CT scan. Patients were instructed to use chlorhexidine mouthwash 0.2% for 1 minute twice a day, starting 3 days prior to the intervention and thereafter for 1 week. Antibiotic prophylaxis with 1 g of amoxicillin and clavulanic acid (Augmentin, Roche, Milan, Italy) every 12 hours was prescribed from the day before surgery to the sixth post-surgical day. Clarithromycin (Klacid, Abbott, Rome, Italy) 500 mg was given on the day before the intervention, and 250 mg twice a day prescribed for one week to patients allergic to penicillin. Surgical procedures were performed under local anaesthesia. Dental implants were installed using a flapless or flapped technique, and full-thickness crestal flaps were raised with minimal extension so as to reduce patient discomfort. In some cases, tooth extraction was needed, and was performed as atraumatically as possible using periotomes and small levers to preserve the buccal alveolar bone.
Extraction sockets were carefully cleaned of any granulation tissue. The implant sites were prepared according to the implant manufacturer's instructions (J Dental Care, Modena, Italy). Tapered implants (JDEvolution, J Dental Care) with internal hex connection and sand-blasted acid-etched surface up to the neck were used for this trial. In general, the implant platform was placed at the crestal level in healed edentulous ridges, and 0.5 to 1 mm below the vestibular bone crest in immediate post-extraction sockets. Anorganic bovine bone (Bio-Oss, Geistlich Pharma, Wolhusen, Switzerland) granules (0.25–1 mm) were used to fill any residual gap greater than 1.5 mm between the implant surface and bone wall.

The final insertion torque was measured using a calibrated torque wrench (JDTorque, J Dental Care) able to perform torque measurement within a range of 15 to 80 Ncm with 5% precision. Implants had diameters of 4.3 or 5 mm and lengths of 10, 11.5 or 13 mm (**TABLE 1**); surgeons were free to choose implant diameter and lengths according to clinical indications. In the test group, platform-switched provisional titanium abutments were placed immediately following the surgical phase. After checking the occlusion, the abutments were cut and modified on an implant analogue if required. The temporary restoration, manufactured prior to the intervention, was then relined in situ with acrylic resin, refined, polished and cemented (Temp Bond, Kerr, Karlsruhe, Germany).

The occlusal surface of the provisional restoration was ground to prevent any occlusal contact with the opposing dentition under static or dynamic conditions. In the control group, healing abutments were attached, and implants were left to heal unsubmerged. Interrupted sutures were placed using a synthetic monofilament thread (Vycril, Ethicon, Johnson & Johnson, Somerville, NJ, USA), and were removed after 10 days. Patients received instruction on oral hygiene, and indications regarding a soft diet, to be adhered to for 8 weeks. Definitive multiple-unit fixed prostheses were fitted 2 months after surgery. An impression was taken with pickup impression copings, and was made in polyether (Impregum Penta, 3M Italia, Pioltello, Italy). In both groups, definitive restorations were fitted with full occlusal contacts.

Patients were subjected to oral hygiene maintenance and prosthesis check-ups every 3 months up to the first year, and thereafter every 6 months.

Outcome measures

The treating dentists involved in the trial made all clinical assessments, and outcome assessors were therefore not blinded.

The primary outcome measures were the following.

- Implant failure: evaluated as implant mobility and removal of stable implants dictated by progressive marginal bone loss or infection. The stability of each implant was measured manually by tightening the abutment screw with a wrench delivering a torque of 30 Ncm. Spinning implants were recorded as failures. After insertion of the defini-

TABLE 1 PATIENT AND INTERVENTION CHARACTERISTICS

	Immediate (n = 40)	Early (n = 40)
Males	13 (32.5%)	18 (45%)
Females	27 (67.5%)	22 (55%)
Implant number	81	80
Mean age at implant insertion (range)	51.8 (39-65)	55.3 (43-65)
Smokers (less than 10 cigarettes/day)	12 (30%)	10 (25%)
Diabetes	1 (2.5%)	2 (5%)
Implants inserted in mandibles	34 (41.9%)	26 (32.5%)
Implants inserted in anterior areas (canine to canine)	6 (7.4%)	8 (10%)

tive restorations, prostheses were not removed to assess clinical mobility of individual implants.

- Any biological or biomechanical complication occurring at the implant site during the entire follow-up time was recorded and reported per study group. Examples of biological complications were: peri-implant mucositis (heavily inflamed soft tissue without bone loss), peri-implantitis (bone loss with suppuration or heavily inflamed tissues), presence of fistulas. Examples of biomechanical complications were loosening or fracture of the abutment screws, and crown fractures.

The secondary outcome measure was peri-implant marginal bone level changes, as evaluated on intraoral radiographs taken with the paralleling technique at implant placement, and at 1 year, 3 years and 12 years after loading. All measurements were made by an independent, blinded assessor (Giovanni Grandi).

Digital radiographs were taken, and Image J 1.42 software (National Institute of Mental Health, MD, USA) was used to measure peri-implant marginal bone levels. The software was calibrated for every single image, based on the known implant diameter. Measurements of the mesial and distal crestal bone levels adjacent to each implant were made to the nearest 0.01 mm, and averaged at patient and group levels. The measurements were taken parallel to the implant axis. The most coronal margin of the implant collar and the most coronal point of bone-to-implant contact were considered as reference points for the linear measurements.

Data analysis

The sample size was calculated to compare proportions in two equally sized groups based on the primary outcome measure of the study (implant failure). The number of patients likely to have at least one implant failure was obtained from a previous study on fully edentulous patients: the proportion of failures in the immediately loaded group was 0.39 compared with the conventionally loaded group[5]. A two-group continuity-corrected chi-squared test with a two-side significance level has 80% power to detect the difference between a proportion of 0.39 and a proportion of 0.04 (odds ratio of 0.065) when the sample size is 52 (26 patients in each arm). The plan involved recruiting 40 patients for each group to compensate for possible drop-outs. Statistical analysis was performed using the statistical package StatView (version 5.01.98, SAS Institute, Cary, NC, USA).

The mesial and distal measurements of the crestal bone level were averaged at each implant, and then at patient and group levels. Differences between groups in patient-level means for continuous outcomes were compared via a t-test. A within-group comparison was performed using a t-test for paired data. Student's t-test was applied to evaluate differences in resorption between the two treatment groups. Comparisons among centres were performed via one-factor analysis of variance (ANOVA). Differences in the proportions of patients with implant failures were compared among centres using the chi-squared test. Differences in crestal bone levels change were compared among centres using t-tests. When necessary, the prevalence of patient characteristics was compared via contingency tables and the chi-squared test. For all analyses, the null hypothesis was rejected at a two-tailed $P < 0.05$.

RESULTS

A total of eighty patients were enrolled in the trial and randomized into two groups: 40 to the immediate loading group and 40 to the early loading group. Further information about non-eligible patients has been described in a previous article[11]. All patients were recruited and tre-

ated from March 2007 to June 2009. The follow-up for all patients was 12 years post-loading (last follow-up June 2021). The main baseline patient characteristics are showed in **TABLE 1**. The distribution of patients across the 5 centres is shown in **TABLE 2,** the lengths and diameters of the implants are described in **TABLE 3**, and the insertion torque in **TABLE 4**.

A total of 161 implants were placed: 81 in the test group and 80 in the control group. One deviation from the protocol occurred: in 1 patient, randomized to the immediate-loading group, three implants were placed instead of two. **FIGS. 1** and **2** show periapical radiographs from two patients involved in the study.

All implants were inserted with the minimum required torque. Twenty-five patients were lost before completion of the 12-year follow up: fourteen patients from the immediate-loading group (14/40, 35%) *versus* eleven patients from the early-loading group (11/40, 27.5%); unfortunately, one investigator (Modena 2) died after the 8-year follow up, and the patients he had treated (eight patients from the test group and eight patients from control group) were unreachable.

Additional dropouts were the following.

TABLE 2 PATIENT DISTRIBUTION ACROSS THE VARIOUS CENTRES

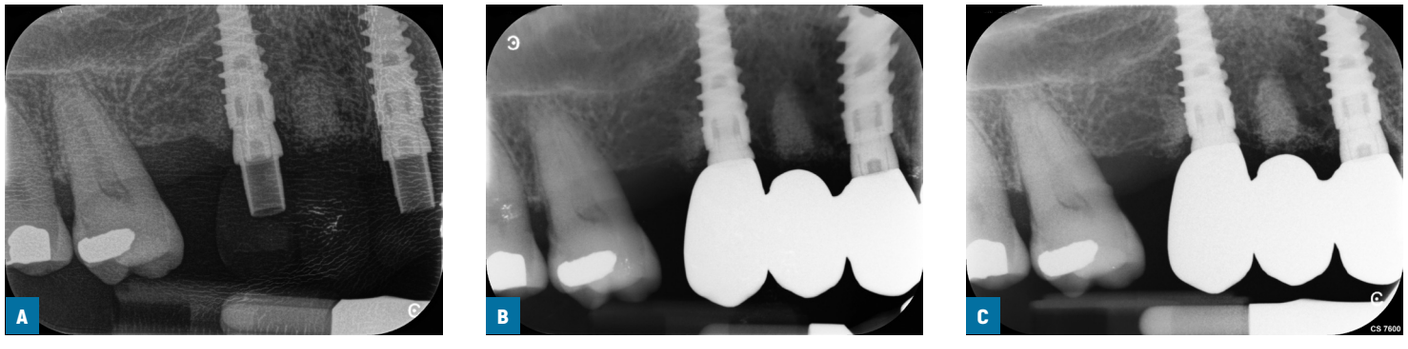
Centre	Immediate (n = 40)	Early (n = 40)
Modena 1	12 (30%)	12 (30%)
Modena 2	8 (20%)	8 (20%)
Bologna 1	5 (12.5%)	5 (12.5%)
Bologna 2	9 (22.5%)	9 (22.5%)
Rimini	6 (15%)	6 (15%)

TABLE 3 IMPLANT LENGTH AND DIAMETER

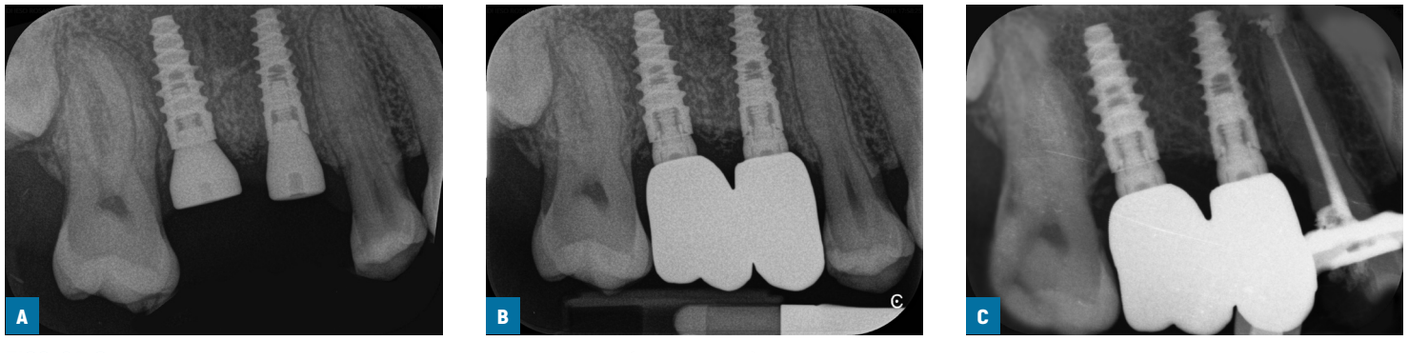
Length	Immediate (n = 81)	Early (n = 80)
10	21 (25.9%)	22 (27.5%)
11.5	34 (42%)	39 (48.8%)
13	22 (27.2%)	19 (23.7%)
15	4 (4.9%)	0 (0%)
Diameter		
4.3	69 (85.2%)	67 (83.7%)
3.7	12 (14.8%)	13 (16.3%)

TABLE 4 FINAL SEATING TORQUE OF THE INSERTED IMPLANTS

Insertion torque (Ncm)	Immediate (n = 81)	Early (n = 80)
30	0 (0%)	2 (2.5%)
35	3 (3.7%)	5 (6.2%)
40	1 (1.2%)	5 (6.3%)
45	4 (4.9%)	2 (2.5%)
50	6 (7.4%)	6 (7.5%)
55	3 (3.7%)	0 (0%)
60	11 (13.6%)	8 (10%)
65	4 (4.9%)	7 (8.7%)
70	10 (12.3%)	17 (21.3%)
75	11 (13.6%)	7 (8.7%)
80	28 (34.6%)	21 (6.2%)



FIGS. 1A-C: *Case 1. Example of one patient randomized to immediate loading (test group): baseline periapical x-ray taken immediately after implant insertion. The implants were immediately loaded with a provisional restoration (A); periapical x-ray taken after the fitting of the final restoration (B); periapical x-ray at 12 years post-loading (C).*



FIGS. 2A-C: *Case 2. Example of one patient randomized to early loading (control group): baseline periapical x-ray taken immediately after implant insertion. The implants were not submerged (A); periapical x-ray taken after the fitting of the final restoration (B); periapical x-ray at 12 years post-loading (C).*

Immediate-loading (test) group

- One patient dropped out due to illness, resulting in her inability to attend further appointments (Modena 1).
- Two patients did not attend the 12-year appointment because they had moved to another city (Bologna 2).
- One patient died after the 6-year follow-up (Modena 1).
- Two patients declined to attend the 12-year follow up (one patient from Bologna 2 and one patient from Rimini).

Early-loading (control) group

- One patient did not attend the 12-year follow-up appointment because he had moved to another city (Bologna 2).
- Two patients declined to attend the 12-year follow up (Modena 1).

Patients were generally healthy, but 3 patients suffered from diabetes. One of these was included in the test group, the other two in the control group. There were no apparent baseline imbalances between the two groups.

Implant failures

Two implants failed in the control group in a female smoker affected by peri-implantitis; implants became mobile after 4 years and were not replaced. There were no statistically significant differences in patients experiencing implant failures between the two groups (patient level, 1/29 *vs.* 0/26, 3.4% *vs.* 0%, difference 3.4%; 95% CI: -0.5;7.3; P=0.339).

Complications

Four complications occurred in the test group and five complications in the control group. There was no statistically significant difference between groups in the number of patients experiencing complications (patient level, 4/26 *vs.* 5/29, 15.4% *vs.* 17.2%, difference 1.8%; 95% CI: -1.7;5.3; P=0.853) or among the four different centres (15.0% *vs.* 18.2% *vs.* 19.4% *vs.* 13.7%, P=0.744).

The following complications occurred in patients from the test group:

- Two patients experienced peri-implant mucositis two years post-implantation, resolved by a curettage and 0.2% chlorhexidine mouthwash;
- One patient's definitive ceramic prosthesis chipped 5 years after loading; the prosthesis was unscrewed and repaired in the laboratory;
- One patient experienced loosening of the definitive prosthesis screw 6 years after loading.

The following complications occurred in patients from the control group:

- One patient experienced peri-implantitis, and both implants became mobile after 4 years and were removed;
- Two patients' definitive ceramic prostheses chipped 6 and 7 years after loading, respectively; the prostheses were unscrewed and repaired in the laboratory;
- One patient experienced peri-implant mucositis at both 5 years and 8 years post-implantation; this was resolved by non-surgical debridement and 0.2% chlorhexidine mouthwash;
- One patient experienced loosening of the definitive prosthesis screw 4 years after loading.

Marginal bone level changes

Both groups gradually lost a statistically significant amount of marginal peri-implant bone (P <0.001) up to 12 years after implant placement (**TABLE 5**). After 1 year, patients in the test group lost an average of 0.42 mm (95% CI 0.25, 0.59) of peri-implant bone *versus* 0.46 mm (95% CI 0.20, 0.72) in control group patients. After 3 years, patients in the immediately-loaded group lost an average of 0.91 mm (95% CI 0.63, 1.17) of peri-implant bone, as compared to 1.15 mm (95% CI 0.81, 1.39) in those in the early-loaded group. After 12 years, patients in the test group lost an average of 1.41 mm (95% CI 0.67, 2.05) of peri-implant bone *versus* 1.62 mm (95% CI 0.96, 2.28) in control group patients. There were no statistically significant differences between the two loading strategies in terms of peri-implant bone level changes at 1 year (P = 0.59; difference 0.04 mm; 95% CI -0.025, 0.105), 3 years (P = 0.67; difference 0.24 mm; 95% CI -0.23, 0.63), or 12 years (P = 0.45; difference 0.21 mm; 95% CI -0.42, 0.84). There were no statistically significant differences in bone level changes among centres (P = 0.55). Twelve years after placement, bone resorption around implants placed in fresh extraction sockets and non-post-extraction implants was compared via post-hoc analysis; no statistically significant difference was observed, the resorption being 1.45 mm (95% CI 1.03, 1.87) and 1.57 mm (95% CI 0.98, 2.06), respectively (P = 0.56; difference 0.12 mm; 95% CI -0.33, 0.57).

DISCUSSION

This RCT aimed to compare the outcomes in terms of implant failure, complications and radiographic bone level changes of immediately-loaded non-occlusal implants *versus* early-loaded implants after 12 years of function in partially edentulous patients. The data collected in this trial show that both loading protocols yielded good clinical outcomes, which were maintained over a 12-year period of time. There were only two implant failures in the early group, both in the same patient, while there were four complications in the immediate group and five complications in the early group. No statistically significant differences were found between the two groups. Patients in the immediate group lost an average of 1.41 mm of peri-implant bone *versus* 1.62 mm in patients in the early group.

One of the most important factors for implant success is primary stability, and movement should be avoided during the healing period, especially in immediately loaded implants. Primary implant stability is closely linked to other factors such as bone quantity and quality,

TABLE 5 MEAN RADIOGRAPHIC PERI-IMPLANT BONE RESORPTION IN THE TWO GROUPS AT DIFFERENT TIME-POINTS

Time-point	Immediately loaded group	Follow-up	Early loaded group	
	Mean bone level (SD)		**Mean bone level (SD)**	**P value**
Baseline (n = 40)	0.01 (0.15)	Baseline (n = 40)	0.05 (0.12)	0.31
12 months (n = 40)	0.42 (0.48)	12 months (n = 40)	0.46 (0.50)	0.59
3 years (n = 38)	0.91 (0.55)	36 months (n = 39)	1.15 (0.54)	0.67
12 years (n = 26)	1.41 (0.64)	12 years (n = 28)	1.62 (0.66)	0.45

implant micro- and macro-topography, and surgical procedure[13-15]. Hence, to be included in the study, implants had to be inserted with a torque ≥30 Ncm.

Immediate and early loading have been widely adopted, especially in patients with mandibles with good bone quality[16]. There are many RCTs comparing immediate, early and conventional loading of dental implants, but there are only two randomized controlled trials with a follow-up period similar to the present study available. Specifically, in a 15-year multicentre randomized controlled trial, Testori et al. analysed peri-implant bone and soft-tissue levels at immediate non-occlusally loaded *versus* unsubmerged early-loaded implants placed in partially edentulous patients. They found no significant intergroup differences in failed implants, complications, peri-implant bone or soft-tissue levels changes. Patients lost an average of 1.75 mm (immediate loading) or 1.44 mm (early loading) of peri-implant marginal bone, and the soft tissue had receded by 0.55 mm and 0.16 mm, respectively, in the two groups at 15 years after loading[17].

In a 10-year randomized clinical study, Merli et al. compared immediate *versus* early non-occlusal loading of dental implants placed flapless. No differences were found between implants loaded immediately *versus* early. The mean bone level at 10 years was 0.9 mm for immediate group and 0.7 mm for early group; the adjusted difference in bone level was 0.1 mm[18].

In the trial reported here, although the provisional restorations of immediately loaded implants were used during chewing, they were not subjected to direct occlusion with the opposing dentition for 2 months in order to minimise the risk of implant failures due to overload. To date few studies are available on the choice between occlusal and non-occlusal immediate loading[7,19-21]. However, a meta-analysis thereof did not find any statistically significant difference between immediate direct occlusal loading and non-occlusal loading[2]. Nonetheless, from a clinical point of view, the authors recommended not placing provisional restorations in direct contact with the opposing dentition, especially in cases such as rehabilitation of the posterior region or insertion of implants with low torque values.

One limitation of this RCT is the small sample size, but unfortunately the centres did not have the capacity to recruit more patients over a reasonable study period. Another limitation is that one investigator died after 8 years, so the patients he treated (eight patients from each group) became unreachable and were therefore lost to follow up. On the other hand, the dentists who delivered the interventions were highly trained. The outcomes were evaluated under real clinical conditions, and the patient inclusion criteria were rather broad, so we would expect similar results in other patients with similar characteristics treated similarly by other clinicians.

CONCLUSIONS

At 12-year follow-up no statistically significant differences in failure rates, complications or bone level changes were observed between implants loaded immediately or early in this RCT.

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